Murray. Ludwig's Angina Complicating Typhoid, American Medicine, 1903.

Post-typhoid Paralysis of the Crico-artenoid Muscle, Transactions of the College of Physicians, Philadelphia, 1901.

Bennet. Laryngeal Perichondritis, British Medical Journal, 1898, vol. i. p. 499.

Cushman. Laryngeal Complications in Typhoid, Nothnagel's Encyclopedia of Practical Medicine, 1902, p. 239.

Duffey. Laryngeal Necrosis in Typhoid, British Medical Journal, 1898, vol. i. p. 499.

Croly. Ibid.

Parsons. Ibid.

Wishart. Post-typhoidal Ulceration and Abductor Paralysis of the Larynx in Typhoid, Philadelphia Medical Journal, 1901, vol. iii.

Griffith. Stenosis of the Larynx in Typhoid, Arch. Pediatrics, May, 1900.

Williams. Laryngeal Complications in Typhoid, Diseases of Upper Respiratory Tract, etc., 1901.

Berggrum. Laryngeal Œdema in Typhoid, Annals of Ophthalmology and Otology, 1896.

Adams. A Case of Typhoid Fever Complicated by Laryngeal Diphtheria, National Medical Review, Washington, vol. vii.

Laryngeal Complications in a Case of Typhoid Fever, Journal of Oto Rhino Laryngol Espa., Madrid, 1898, vol. i.

A Case of Laryngeal Perichondritis during Typhoid, Ejened, St. Petersburg, vol. vii.

Lambert. Laryngeal Complications in Typhoid, Progressive Medicine, 1901, p. 200.

Mayer. Laryngeal Perichondritis Resulting from Typhoid, Transactions of the American Laryngological Association, May, 1903.

Mayer. New York Medical Record, September 17, 1904.

ANGIONEUROTIC ŒDEMA INVOLVING THE UPPER RESPIRATORY TRACT.*

By Thomas H. Halsted, M.D.,

PROFESSOR OF LARYNGOLOGY AND OTOLOGY, SYRACUSE UNIVERSITY MEDICAL COLLEGE.

Angioneurotic œdema, as defined by Collins,[1] is a "vasomotor neurosis or an angioneurosis, characterized by the appearance of circumscribed swellings on various portions of the surface of the body and the mucous membranes, by preference the face, throat, and extremities, without apparent cause or premonition, and non-inflammatory in character."

As it affects the skin, the disease was first described by Quincke as "An Acute Circumscribed Œdema," and from his first description the disease was early called "Quincke's disease." Shortly after Strübing[2] described it as affecting the throat, calling it an "angioneurotic œdema of the throat," regarding it as a vasomotor neurosis, developing rapidly, without fever, after exposure to cold or some traumatism.

The disease is frequently described in books on diseases of the skin under the heading of urticaria. Crocker regards it simply as one of its varieties, giant urticaria. Stelwagon treats of it under a heading of its own, recognizing its similarity in many cases to urticaria, but in other cases says it is entirely or sufficiently independent of it to warrant its description under its own title. Montgomery and Hyde say it should not be confused with erythema multiforme, erythema nosodum, or giant urticaria. Kaposi and Shoemaker refer to it as a distinct disease, but closely allied to giant urticaria, with which, however, it is not to be confounded.

---

* Candidate's Thesis, American Laryngological Association, June, 1905.

Osler[3] has been greatly interested in the disease, and in 1888 reported a case of angioneurotic œdema, investigating particularly the question of heredity. Since then he has made three notable communications,[4] reporting in the three papers 29 cases, and in the last one reviewing them all under the title of "The Visceral Complications of the Erythema Group of Skin Diseases."[5] In this paper, and based upon his cases, he shows very conclusively that simple erythema, erythema exudativum, erythema nodosum, certain of the purpuras, urticaria, and angioneurotic œdema, are all very intimately related; that the lesions of any or all of these various affections may, and often do, occur in one individual during the course of his disease, or even during one attack of the disease, so that at one time one observer might make a diagnosis of urticaria; in a subsequent attack another may call it angioneurotic œdema, or during another attack peliosis rheumatica. In a word, a patient observed for a number of years is likely to present at one time or another a variety of lesions, all of them, however, vasomotor neuroses, and so he prefers to classify them under the general head of "the erythema group of skin diseases." He divides the complications into two great groups, the angioneurotic and the inflammatory. To the angioneurotic belong the swellings of the fauces, œdema of the glottis, changes in the bronchial mucosa, causing asthma and the colic due to the œdema of the gastrointestinal tract. The inflammatory group are more serious and include endocarditis, pericarditis, pleurisy, pneumonia, and nephritis.

It is unfortunate that so many writers in reporting their cases have used the term "urticaria" in describing "angioneurotic œdema," this being apparent from their description of the lesions and it has led to much confusion.

While all text-books on the skin describe this disease under one heading or another, and nearly all refer to the fact that the lesions affect the tongue, fauces, and larynx, yet text-books on the nose and throat, with few exceptions, have neglected any reference to or description of the disease in any way. This is particularly so in the case of American text-books. Of sixteen of these latter, but three (Kyle, Posey and Wright, and Bosworth) make any mention whatever of the disease, and in but one (Bosworth) is there any description at all.

Case I.—J. B., male, aged twenty-four years, single, blonde, of a marked neurotic temperament, consulted me at 7 o'clock in the morning of April 4, 1893, twelve years ago, because of difficulty in swallowing and speaking, and of a swelling in the throat, which had come on suddenly three hours before, wakening him from sleep. He had gone to bed feeling perfectly well.

The open mouth, fixed jaw, thick speech, and evident pain and discomfort in speaking at once suggested quinsy.

On examination I found a pale yellow, almost translucent, œdematous swelling of the right side of the fauces, almost completely filling this half of the faucial opening. The parts involved were the anterior and posterior pillars, the right half of the velum palati, the uvula, and the lateral wall of the pharynx of the same side. The tonsil itself was not swollen, though pushed out as in quinsy. Except for the swelling there were none of the signs of inflammation, the color being a pale yellow, the contour alone resembling peritonsillitis. The larynx was normal, except for the slight congestion of the vocal cords; tongue not swollen, but thickly coated; some earache. He complained of a slight dyspnœa, and marked dysphagia. Temperature normal, pulse 90, constipated. Has now and has had some gastric disturbance. Urine 1022, acid, no albumin. He gives this history:

About a month ago, for the first time in his life, there appeared, without apparent cause, a localized œdematous swelling, without pain or redness, just above the olecranon of the right elbow, followed the next day by a similar swelling over the biceps of the same arm. These were soon followed by like swellings in both feet after a long walk, then in both hands; in a day or two another swelling made its appearance in the left shoulder following a bruise. The next swelling was in the fauces somewhat similar to the present one, except that it was on the opposite side and was very much smaller. This, as had those in the skin, disappeared within twenty-four hours of the onset, and he had a respite for three or four days. The next was serious enough to threaten life. At this time there came on rapidly great difficulty in breathing, rapidly increasing, so that he immediately consulted the laryngologist who had been treating him, and who had the previous day applied a zinc chloride solution to the larynx. After examination he was told there was an œdema of the larynx, pale in color, and in appearance resembling a polypus, but which his physician regarded as urticarial. The dyspnœa was so great that it was feared tracheotomy might be required at any moment. However, without any local treatment beyond the use of a cocaine spray and the internal use of salines, the dyspnœa gradually diminished and the swelling disappeared entirely within thirty-six hours.

His tongue and right cheek were next affected. A day or two later, following a bicycle ride, there came on quickly a swelling of the genitals, the scrotum and penis being enormously swollen, as well as the inner aspects of both thighs, extending from the anus behind to Poupart's ligament and over the hypogastrium in front. This swelling was not painful beyond the feeling of distention; did not burn or itch, and was not reddened. It kept him in bed, and disappeared in forty-eight hours. From this time until I saw him he had several minor œdematous swellings on the hands and feet.

I scarified with a small bistoury the mucous membrane in a number of places, causing immediate relief to the discomfort and distention, and a marked subsidence of the œdema. Ordered discontinuance of cocaine and antipyrine spray, which he was using, and prescribed saline purgatives. Nine hours later the swelling in the throat was almost entirely gone; pulse and temperature normal. Feels well, but there has suddenly appeared since morning an œdema of the upper and lower lids of the right eye, closing it. Two days later there was no swelling whatever in the throat, and none in the eyelids, but one is just beginning over the left mastoid.

The patient, who had come on a visit to his parents from Brooklyn the night before I saw him, now returned, and I did not see him again for several years; but from a letter a few weeks later learned that he had a few slight swellings in hands and feet, but nothing serious. In writing he called my attention to the fact that all three acute attacks in the throat followed the free use of the cocaine and antipyrine spray, which had been prescribed for nasal obstruction, of which he had been having a great deal of late.

These different swellings of the throat and of the skin were all characterized by coming on suddenly; were circumscribed, œdematous, did not pit on pressure, and there was an absence of redness, heat, pain, and throbbing, not at all resembling an urticarial wheal, excepting in the suddenness of occurrence and subsidence.

Family History. On mother's side, grandmother and her sisters had, as children, urticaria severely. One uncle has an attack of it after eating canned fruit. This uncle's son as a child had the disease so badly that "he would go into spasms." Patient's mother, five years ago, had urticaria off and on for six months, being under medical care continually for it. It disappeared after a successful perineal operation. The mother's family have for years regarded urticaria as a family disease. They are also distinguished among themselves by a peculiar gastric affection, which they designate as the "S—— stomach." No other family history of gout or rheumatism.

The attack in which I first saw this patient occurred twelve years ago. He was at that time a director of a gymnasium. He is now a physician, and in reply to a letter written him recently, he writes me, under date of April 3, 1905, that up to about two and a half years ago he had considerable local trouble in the head and throat of a catarrhal nature, but without the occurrence of the previous œdema experienced when he was under my care twelve years ago. On two separate occasions five years ago he had serious attacks of intestinal hemorrhage. These were preceded for a day or more by a feeling of weakness, depression, weight in the epigastrium, followed by a condition of collapse resembling a moderate degree of shock. This was followed in a day or two by a profuse tar-colored stool, staining the water red, and with it much prostration for a few days, followed by a gradual recovery. For seven years, from 1896 to 1903, he had considerable intestinal trouble, the principal manifestation being the enormous accumulation of gases, which would rise into the stomach and be belched up, very little passing through the bowels. For the past two years he has been gradually improving, very little of the catarrhal trouble in nose and throat, and the gastrointestinal difficulty gradually but steadily lessening.

This patient has had the disease twelve years. He had the typical angioneurotic œdema of the skin, fauces, larynx, and nose twelve years ago, almost requiring tracheotomy on one occasion, and in the nose so badly that for a time the only relief obtained from the nasal obstruction was through the use of cocaine. In addition to the lesions affecting the skin and upper respiratory tract, he had, five years ago and again two years ago, evidences of the same disease affecting locally the gastrointestinal tract, as well as hemorrhages, probably due to purpura, from the intestinal mucous membranes.

His family history shows the influence of heredity in a marked manner. Being a physician, he was greatly interested in the cause of the various attacks, but was never able to determine the immediate cause, excepting that on two occasions he thought the attacks followed traumatism. He never discovered that any particular article of food produced an outbreak.

CASE II.—A. M., aged fifty-five years, a manufacturer; of a decided nervous temperament. He has been under my observation off and on for nasal and throat difficulty for about six years. He came under my care first because of nasal obstruction, which would come on suddenly and as quickly disappear. There was no periodicity noticed about it, and it occurred at all seasons of the year; would last a few hours or days, no sneezing, and none of the usual signs of a cold in the head, nor did it act like hay fever. The peculiarity was that this obstruction came on usually during the night and by morning was gone. He also had suddenly arising swellings in the throat; the uvula and soft palate would become œdematous, and the dyspnœa would waken him from sleep, so that he was often compelled to sit up to breathe. The voice would become thick and husky at times. There was no oppression or rales in the chest. He insisted the dyspnœa was not that of asthma, but due to the swelling in the throat. The condition would usually begin to improve in a few hours, and in twenty-four to thirty-six would usually have disappeared. An examination of the nose showed at times a rather pale œdematous infiltration of the turbinates, sometimes of one, sometimes of all; but on another visit there would be no sign whatever of any thickening, hypertrophy, or œdema. The only constant abnormality appeared to be a thickening of the septum opposite the middle turbinate on the right side. This thickening of the septum and the anterior end of the middle turbinate I removed, and while it improved his nasal breathing, it did not do away with or lessen the frequency of these suddenly occurring obstructions. These nasal and pharyngeal swellings would be preceded, followed, or there would occur at the same time, pale yellow swellings of the skin of various parts of the body, notably the eyelids, the scrotum and penis, the feet, and hands. These attacks would last from a few days to two weeks, and he might be as long as two months, and occasionally has gone six months without an attack. They have been recurring during the past eighteen years. He is at the present time having an attack, and a description of it will answer for all.

It is two months since the previous outbreak. A few evenings ago, while attending a banquet, the left side of the tongue began to swell; on reaching home he took a large dose of alkalithia, hoping to ward off the attack. The following morning he came to my office with the right upper eyelid œdematous and swollen, and the eye closed; it was pale, yellowish, did not burn or itch. No throat or nasal lesions, and the swelling of the tongue gone. That night he awoke, finding the nose obstructed and the throat swollen, and in the morning I saw him. There was a patch of œdema larger than a bean on the left side of the hard palate, and a pale œdematous swelling involving the uvula and the left posterior pillar of the soft palate, extending down the lateral side of the pharynx to the pyriform sinus. The mucous membrane of the left arytenoid was as large as a cherry. The obstruction in the nose had disappeared and there were no œdematous spots here. There was no pain in the throat, but merely a sense of fulness, with slightly obstructed breathing. On the skin there was a swelling under an inguinal truss and the scrotum was swollen. There is, and has been, no disturbance with digestion; bowels regular. Dr. Dutcher examined the urine and reported as follows: "Color pale amber, slightly cloudy, faintly alkaline, specific gravity 1023, no albumin; no sugar; urea, 2 per cent.; slight indican; no excess of uric acid. Microscopic examination showed mucus and an occasional epithelial cell." The œdema in the throat and skin entirely disappeared during the day, and there was no reappearance for three days, when the right upper and lower eyelids became swollen and closed the eye. This is a typical attack, such as he has been having at intervals for the past eighteen years. The swelling in the feet prevents his wearing his shoes and confines him to the house at times. The dyspnœa is often alarming, but he has never had to call a physician during the night. He says the attacks are becoming less frequent than formerly, and attributes this to the fact that he thinks he knows when they are coming on by his urine becoming more acid, and he at once resorts to alkalies. He has watched his diet during all these years, and has finally given up thinking any specific kind of food provokes the attacks, as he has from time to time excluded almost everything without that making much difference.

Family History. He has two children, both of whom have been under my care. The son had asthma until ten years of age, and I removed the adenoids because of this ten years ago and with an apparent relief of the asthma. I have not seen him since, and his father says he has had no attacks in several years. He has never had urticaria or the angioneurotic œdema as his father.

The daughter had repeated attacks of what I thought was rheumatic pharyngitis, which recurred with great frequency. I was never satisfied with my diagnosis, and as she was under my care before her father, it did not occur to me that the difficulty might be one allied or related to angioneurotic œdema. Her father says she never had hives or his disease.

The patient had one brother, who, during the latter years of his life, suffered repeatedly and severely from attacks of what were diagnosed as "gallstone colic," and had outbreaks of a skin disease, said to have been eczema. Two years ago he fell, injuring one of his knees. One month later, while in apparently good health, after being at stool, he suddenly fell and died immediately. A searching autopsy was made, but failed to find any cause of death. An embolus in the brain was suspected, but was not found, and, as the case came into court through an action to recover from the accident company, the cause of death was thoroughly canvassed. The autopsy revealed no cause whatever from the gallstone colics from which he had suffered. In the light of the angioneurotic disease in my patient, his brother, the history of gallstone colics for years, without a discoverable cause at autopsy, and the fact that, as Osler has reported, suddenly arising œdemas occur in the brain, it is fair to question whether this might not have been such a case.

The next case appears to be a genuine one of urticaria, affecting the pharynx, larynx, and probably the nose, and shows both the similarity and the difference in the lesions and subjective symptoms of angioneurotic œdema and urticaria.

Case III.—E. R., aged thirty-five years, merchant; of a highly nervous temperament, consulted me June 24, 1904, because of what he called "a sudden swelling of the tonsils and a feeling of impending suffocation at such times." He snored a great deal at times and at others not at all. The day before consulting me he had entertained a number of men at his country house, which had made him very nervous and had drunk quite a little beer, and that night thought he would die before relief could be had because of the sudden swelling of his throat and obstructed breathing. This came on in a moment and gradually subsided, passing off in half an hour. These attacks of dyspnœa and the desire to constantly swallow have been occurring for about five years. The first attack followed an outbreak of what he called hives all over the body, including the face and lips, which became greatly swollen. Since that first attack there have been no skin lesions. The swellings in the throat had, of late, been coming on every day or two, though at times he would go a couple of weeks, or even a month. He has been treated by a number of physicians without relief. On examination I found a deflected septum, partially obstructing the left nares, tonsils somewhat enlarged, and the uvula slightly elongated. I could discover no œdematous swelling in the throat, nor any other local trouble. He was not having any symptoms at the time of the examination. He had never had asthma or colic. The urine examined the next day was amber, clear, highly acid; specific gravity, 1030; urea, 4 per cent.; no albumin; no sugar; no indican; a very large excess of acid; no casts; no pus.

I made a diagnosis of angioneurotic œdema, prescribed alkalies and large quantities of water, and explained the nature of the trouble, and asked him to come in again on recurrence of the first attack. He did not return, however, and I did not see him again for nine months; in the mean time he had been under the care of several specialists, one of whom partially excised one tonsil, without, however, affecting the sudden swelling of the throat; another proposed uvulotomy, and the third assured him his symptoms were entirely nervous and largely imaginary. When I saw him recently he was having what he called an attack. He came to my office greatly excited; said his throat felt as though it would close up, and he could not breathe. He was greatly alarmed, and I expected to find a great deal of swelling. On examination, however, the tonsils, soft palate, and uvula and larynx were entirely normal, and I was about to conclude that my diagnosis of nearly a year ago was wrong, when I discovered, with the mirror, on the posterior wall of the laryngopharynx three elevations about the size of a split pea. They were raised above the surface, red, not at all œdematous in appearance, but resembled the wheal of urticaria as seen on the skin. Irritating the membrane half a dozen other elevations soon appeared in size from a pinhead to larger than a pea. The patient said there was no pain, no burning, but a sense of the enormous fulness, and he could hardly believe my statement of the size of the swellings. They were evidently urticarial wheals. In him they would be produced by any slight pyschical irritation or annoyance, such, for instance, as being kept waiting at the telephone, or a person with whom he had an appointment being late, or the unexpected meeting of a friend. These attacks would come on immediately, so that he could not speak for a few moments, but would clutch his throat, begin to swallow rapidly, often to the great consternation of the person with whom he was attempting to converse. An attack would begin often with the sense of burning at the end of the penis, with the desire to urinate, and then this feeling of swelling in the throat would come on.

Family History. His father died a few years ago, and as far back as the patient can remember he suffered from colic, walking the floor nights repeatedly, suffering great pain and the belching of gas because of it. He was said to have had "nervous dyspepsia." He had never had asthma. He died after five days' illness of acute uræmic poisoning without a previous history of nephritis.

A sister of the patient has had urticaria twice during the past two years. She has had a great deal of indigestion with pyrosis.

This appears to be a genuine case of urticaria affecting the pharynx and larynx and the nose. That it may be easily overlooked is seen by the fact that within a year three different specialists who saw him failed to appreciate the condition, probably because no lesions were present when he was examined. Goodale[6] states that urticaria, although observed upon the mucous membrane of the tongue, does not appear to have been found upon the mucous membrane of the nose or throat. Certainly these throat lesions of his resemble the wheal of urticaria observed on the skin. The amount of local irritation and the subjective symptoms produced were out of all proportion to their size, in this respect greatly differing from the lesions of angioneurotic œdema, as seen, for instance, in the throats of Cases I. and II., in which there were ten times the amount of swelling and mechanical obstruction without anything like the amount of subjective symptoms.

The acute circumscribed swelling of angioneurotic œdema, as it appears in the mucous membranes of the respiratory and the gastrointestinal tract, appears to resemble that on the skin. It comes on suddenly, in a few moments or sometimes minutes, without warning, while the patient is asleep or awake, and the symptoms it produces seem to be largely due to mechanical obstruction. In the nose, the symptoms are those of obstructed breathing, not much sneezing, and no excessive secretion, differing in this respect from hay fever, but resembling it in the suddenness of occurrence and subsidence. Doubtless many cases of this disease affecting the nose are diagnosed erroneously as hay fever, which disease it closely resembles, both in its etiology and pathology. Both are vasomotor neuroses, both are markedly hereditary and occur in persons of neurotic temperament, while the œdema of angioneurotic œdema is usually transient, lasting from a few hours to a day or two; that is not always the case. Bloodgood[7] has reported what appears to be a genuine case of this disease, which he calls "angioneurotic erythema persistens," in which the parts involved in the œdema were the mucous membrane of both maxillary sinuses and the skin of both cheeks. The œdema persisted for months. He opened both antræ through the canine fossæ, finding the mucous membrane greatly œdematous. The relief following this operation was but temporary, the erythema and œdema recurring until neurectomy of both infraorbital nerves was done. This gave permanent relief, although the same condition appeared later on the skin of the abdomen.

Osler has also reported cases in which the œdema persisted for a long time. Some of these cases of what are sometimes called perennial hay fever may be those of this disease in which the swollen and œdematous mucous membrane of the nose is not transient but persists. Haviland Hall says: "Urticaria is frequently associated with hay fever," and there is certainly a family likeness between hay fever, on the one hand, and urticaria and angioneurotic œdema of the nasal mucous membranes on the other.

The relation of angioneurotic œdema, and, more particularly urticaria, to asthma has been frequently noted. F. A. Packard[8] reported 3 cases of his own in which attacks of asthma alternated with outbreaks of urticaria on the skin, the cough and dyspnœa being relieved upon the occurrence of the hives, and upon a subsidence of the latter a return of the asthma. The asthma was caused apparently by the presence of wheals on the bronchial mucous membrane. Packard made a thorough search of the literature, and, in addition to his own cases, found and abstracted the reports of 34 other cases in which there was a close connection between urticaria and asthma. Throughout his paper he uses, unfortunately, it seems to me, the term "urticaria" to include "angioneurotic œdema."

In a case of asthma under the writer's care twelve years ago, the patient, a man, aged sixty-five years, had had the disease for about thirty years, and had been under the care of many excellent men, but never received more than temporary relief. He was referred to me because of a possible nasal cause, and I found the mucous membrane of all the turbinates hypertrophied, gray in color, at times greatly œdematous, obstructing the nose completely, and at such times the asthmatic dyspnœa was always greatest. There were no polypi and the septum was straight. He was scarcely ever entirely free from dyspnœa during the year I saw him, and at times, both day and night, in his office or on the street, the dyspnœa was so great that he was a most pitiful object. I cauterized his turbinates as well as removed the inferior borders of both lower turbinates, giving him temporary relief only. The asthma soon recurred as badly as ever, and we agreed that the nose was certainly not an important etiological factor. On one occasion he came to the office with one eye closed from an acute circumscribed œdema, and a number of similar œdematous patches on the face and scalp. They were not red, did not pit on pressure, nor did they burn or itch. On inquiry, he said he frequently had these outbreaks, usually on the head, and to which he paid no attention. I failed to appreciate at that time the probable relation of the asthma and the skin lesions. It is probable that his asthma was due to an angioneurotic œdema of the bronchial mucous membrane, which had become more or less persistent.

As it affects the larynx, angioneurotic œdema becomes immediately a serious affection. It appears to come on during the night while the patient is asleep. Such was the case with two of my patients. It is entirely probable that many obscure and sudden deaths, occurring during the night, are of this nature, and an autopsy, unless this cause was looked for, would fail to find the cause. During the past few years cases are reported by Woodbury,[9] Hallock,[10] Leddermen,[11] Taylor,[12] Chittenden,[13] Ballenger[14] and others, in which a threatening dyspnœa from this cause occurred. Fatal cases are reported by Osler and Griffith.

Griffith's[15] case, in which both father and daughter died of œdema of the larynx from this disease, is reported in the *British Medical Journal*, June 14, 1902, and should be read in its entirety. He reports the case as "Hereditary Localized Œdema."

"The patient, a woman, was first seen by him in 1886, when she was eighteen years of age, because of dyspnœa, hoarseness, and dysphagia, and œdema of the arm and hand. The œdema involved the epiglottis and aryepiglottic folds, obscuring the view of the vocal cords. Tracheotomy was considered, but did not become necessary, and in a few hours the œdema disappeared. She gave a history of having had these transient œdemas, affecting all parts of the body, from birth. There was no periodicity in their occurrence. There was no history or evidence of any other disease, excepting that she was subject to bilious attacks.

"Her father, from his earliest infancy, had the same kind of swellings, and on three occasions they affected his throat: the first attack at the age of twenty-one years, the second a few years later, and the third at twenty-nine years, when he died as a result of it. In this last attack he came home from work, said his throat was swollen, and his physician was sent for. He came, but returned to his office for something to relieve him, but before his return the patient became suddenly cyanotic and died, asphyxiated.

"For sixteen years, from 1886 to 1902, Griffith saw his patient during many attacks affecting different parts of the skin and throat. The swellings were diffuse or circumscribed, usually pale, sometimes pink, did not pit on pressure, and were never bullous or vesicular. Twice the laryngeal dyspnœa was alarming. The tongue and buccal mucous membranes were at times the site of the œdema. The swelling came on suddenly, without warning, and almost as quickly disappeared. Finally, she had an attack, which proved fatal. At 10.30 A.M. she told her mother her throat was swollen, but that it was subsiding. At noon her husband came home, found her sitting on the floor amusing her child by spinning a top, and apparently free from dyspnœa. Suddenly she dropped the top, tried but could not speak, clutched at her throat, got blue in the face, and died at once. Her mother, who was present at her death, said she died exactly as had her father before her. Griffith saw her a half-hour after death. The features were livid, tongue protruded, some fulness about the neck. The autopsy showed the larynx to be very œdematous, tense, and pale, and the sides of the laryngeal cavity in contact with each other. Transverse sections of the larynx showed that the œdema affected not only the mucous membrane, but the underlying deeper connective tissues and muscles. The œdematous fluid was serous, untinged with the coloring matter of the blood, and the tissues covering the true cords were decidedly affected."

The etiology of this peculiar disease is not at all clear. There are certainly three and perhaps four main etiological factors. Heredity is clearly shown in the classic case of Osler, reported in 1888, in which the disease appeared in five generations, and of the thirty-nine members of this family nineteen had angioneurotic œdema, two dying of œdema of the glottis. Griffith's case, just reported, is a striking one. All of my cases show the element of heredity. The peculiarity transmitted, Osler[5] says, must be either a morbid susceptibility of tissue or an inherited peculiarity of metabolism, or both combined. The individual attacks are probably provoked by some toxin produced within the body, as in the gastrointestinal tract, or in some other organ or tissue of the body, or it may be introduced from without. Gout and rheumatism are often mentioned as causes, but it is very doubtful if there is any connection. It is more probable that this disease is often mistaken for manifestations of gout and rheumatism. A certain poison or a certain kind of food may cause an attack in one person and not in another, or it may not produce a second attack in the same individual. My patients arrived at this conclusion in their own cases. Strawberries, fish, coffee, ice-cream, contact with a jelly fish are all given in the reports of cases as causes, but these cases are almost always simply the reports of single attacks. Exposure to cold and traumatism, worry, anxiety, mental excitement and fright; are doubtless all immediate causes for outbreaks. Antitoxin, as will be referred to later, is probably one of the various causes. These patients are invariably of a marked neurotic temperament. An interesting and an important question is as to the local condition determining, in a predisposed individual, the localization of the lesions, and Osler seems to think this is an important one in any individual case.

Collins[1] found that in 83 cases studied by him, the lesion first appeared in the larynx six times. He says the occurrence on any particular part of the skin or mucous membrane predisposes that part to other attacks.

There has been much question as to whether the colic, which occurs so frequently in the course of the disease, is the cause or the result of the outbreak as it appears on the skin or in the throat. There is no doubt but that in mostly all cases the colic is the effect of the acute œdema localized in the stomach or intestinal tract. Morris[16] reports a case in which a portion of the gastric mucosa became detached in using the stomach-tube. It was examined histologically and showed an extreme œdema of the interstitial tissue, the lymph spaces and vessels being enormously dilated. The abdomen has been opened for supposed appendicitis when the condition was one of angioneurotic œdema of the intestinal mucous membrane.

The histological examination in Griffith's case of fatal œdema of the larynx showed that the œdema involved not only the mucous membrane, but the deeper connective tissue and underlying muscles. Crocker says that everything points to the disease being primarily a vasomotor disturbance, direct or reflex, central or peripheral; that a spasmodic contraction of the vessels is followed by a paralytic dilatation and stasis or retardation of the circulation in the papillary layer of the skin. Serous exudation then ensues, producing acute œdema. The same thing occurs in the mucous membranes and readily explains the sudden œdema and enormous swelling that comes on in a few seconds or minutes.

This same kind of œdema occurs in the brain and in the kidneys and probably in every organ or tissue of the body. Gruss[17] reports a case in which acute circumscribed œdema caused an acute retrobulbar œdema producing proptosis, and associated with cerebral symptoms. Osler's Case XV. had repeated attacks of aphasia and hemiplegia, the lesions on the skin being those of purpura, urticaria, and angioneurotic œdema during the fourteen years of the disease.

Ten days after the injection of antitoxin, given for prophylactic or therapeutic purposes, eruptions on the skin occur in a considerable percentage of the cases injected. These eruptions belong to the erythema group and are in order of their frequency, urticaria, erythema, purpura, angioneurotic œdema. The joints frequently become swollen, and there are evidences of acute swellings in the mucous membranes of the respiratory and gastrointestinal tracts.

Antitoxin from the same bottle may be injected into several children, and yet but one may have a skin eruption develop later, showing that the serum is not alone at fault, but that there exists in the affected patient a "peculiar susceptibility of tissue" or an inherited tendency toward one of the erythematous diseases; the antitoxin or something in it being simply the poison that provokes the attack in that particular person. Morse[18] reports a case in which, five days after a prophylactic dose of 500 units, the child complained of chilliness; prostration, vomiting, and œdema of the uvula and pharynx, the acute symptoms subsiding in thirty-six hours. Two years before this same child, after a prophylactic dose of 700 units, developed an urticaria of the skin.

It can readily be seen that when diphtheria exists in the throat, an acute œdema developing during the course of the disease would be attributed to the diphtheritic infection rather than to the antitoxin injected a few days before, and yet it might be due entirely to the latter. From our knowledge that angioneurotic œdema and urticaria occur in the throat, there is no reason to suppose that antitoxin causes these lesions in the skin and not in the fauces, pharynx, or larynx. There is every reason to suppose it does, and it is quite presumable that some of the suddenly fatal dyspnœas occurring in diphtheria are the result of the remedy operating on a peculiarly susceptible individual rather than to the disease diphtheria. The real cause of death in such cases would be overlooked, being masked by the disease. It is possible that the local lesions of diphtheria, as well as the toxæmia, might prevent the development in the throat of lesions which the antitoxin might, however, produce on the skin.

The cases which have attracted most attention have been those suddenly occurring deaths immediately following the injection of antitoxin, and usually in persons who did not have diphtheria, but were given prophylactic doses because of their exposure. The cause and effect here are not open to much question, but there has been much discussion as to how and why the antitoxin caused death.

It appears to the writer that in these cases the children have probably an inherited tendency to angioneurotic œdema, that the antitoxin has been the exciting cause of an attack, and that the swellings have occurred in the larynx or the lungs, producing a sudden œdema that causes asphyxiation, or the œdema may have occurred in the medulla or the brain, causing a paralysis of the respiratory or cardiac centres with resulting death.

For instance, Halderman[19] gave a prophylactic dose of antitoxin to a five-year-old child, who did not have diphtheria. It was asleep when the injection was given and almost immediately the lips began to puff up and in five minutes breathing ceased. Ninfong[20] gave a fifteen-year-old boy a prophylactic dose of 1500 units. Ten minutes later the boy became pale, extremities numb, cyanosis developed, the cheeks became swollen, and free vomiting occurred. Nitroglycerin was given and artificial respiration was resorted to, but the boy died thirty-five minutes from the time of injection. Prof. Langerhans'[21] son was given a prophylactic dose of antitoxin, and almost at once he began to vomit and soon died of suffocation. The autopsy revealed the trachea and bronchi filled with stomach contents and the uvula swollen. Adamkiewicz thought death was due to shock or pain resulting from the forcible injection under the skin of a large amount of fluid. Langerhans insisted that death was due to the poisonous action of the serum upon a healthy subject when unneutralized by a pre-existent toxin.

These cases would seem to have had an acute circumscribed œdema; in the first case of the lips and probably of the larynx;

in the second of the cheeks, the stomach, and the larynx; in the third of the uvula, and probably of the stomach; in each case the œdema coming on within a few minutes and causing death in from five to thirty-five minutes. None had diphtheria, all having received prophylactic doses.

Kortright[22] gave a sixteen-year-old girl 10 c.c. Behring's antitoxin, making the injection in the left side of the abdomen. She immediately said she "felt a lump in the stomach," and Kortright assumed she meant that she felt the swelling of the injected serum under the skin; but it is equally probable that what she felt was an acute swelling in the gastrointestinal tract. Five minutes later she complained of tingling and became restless, and immediately had a general convulsion. This was followed by general tonic and clonic convulsions, opisthotonos, cyanosis, and cessation of breathing. Artificial respiration was kept up till heart ceased in three minutes, death occurring in eight minutes from time of injection. An autopsy made eighteen hours later showed the brain and meninges, kidneys, and liver all markedly congested. No foreign body in larynx or trachea.

In Applegate's case, a boy, aged four years, having diphtheria, was given 15 c.c. antitoxin. One hour later he became very restless, vision completely lost, and three hours after injection died in convulsions.

Kortright was of the opinion that his case died because of something undiscoverable connected with the antitoxin or the injection. It is probable that had another child received the same injection nothing untoward would have followed—there being in his case the unfortunate combination of a predisposed patient and an exciting cause. In these 2 cases the localized œdemas were probably in the brain.

If these statements regarding antitoxin be true, it is not a reason or an argument against the use of this specific in the treatment of diphtheria, because it has saved thousands upon thousands of lives which otherwise would have been lost and has probably caused the death of but a very few. It is, however, an argument against the indiscriminate use of antitoxin for prophylactic purposes, because a single death from its administration in a person who has been simply exposed and had not contracted, and might not contract, the disease is frightfully deplorable. When it is used prophylactically, the previous personal and family history of the patient as regards the erythematous skin diseases should be inquired into, and if this develop the presence of or tendency to any of these diseases, then the antitoxin should be withheld until diphtheria actually occurs, or at least until a bacteriological examination of the throat in such an exposed person shows the Klebs-Loeffler bacillus.

Some makes of serum seem to have a larger percentage of skin eruptions follow than others, and we see much less of these eruptions now than three or four years ago, showing apparently that the present methods of preparing and "ripening" antitoxin is eliminating some of its deleterious properties, and it may be that in the future antitoxin may become inert as a cause in predisposed individuals, of the production of the erythematous lesions on the skin and mucous membranes.

The treatment of angioneurotic œdema as it affects the upper respiratory tract may be divided into the management of the various acute attacks as they arise, the correction of any local disease which may possibly determine the localization of the lesions or œdemas in the air passages, and the treatment of the constitutional disease back of the attacks. Of the last I have nothing to say beyond the fact that each individual case must be studied by itself, and if possible the underlying cause found and, if it can be, corrected. Osler has called particular attention to the fact that of his 29 cases of the erythema group, 24 per cent. finally died, 5 of the 7 deaths being due to uræmia. He has never seen, however, a case of pure angioneurotic œdema develop nephritis, and the fact is that cases in which angioneurotic œdema is the only lesion throughout the course of the disease are very few. For eighteen years my Case II. has apparently been such a case.

The treatment of the localized œdemas in the fauces, pharynx, and larynx would depend upon the severity. I have used both adrenalin and cocaine locally with apparent benefit, and in more severe cases, scarification of the pharyngeal and laryngeal œdemas. Should the dyspnœa increase and threaten life, tracheotomy should be done without hesitation or delay. Ice locally is probably contraindicated and might add to the œdema. Delbril advises brisk friction of the skin to induce an attack of urticaria on the skin when there is œdema of the larynx. Packard's cases of asthma would bear out the wisdom of this. Quiet in bed, reassurance, and, as far as possible, the removal of anxiety are important. These patients are highly neurotic, and fright alone might precipitate a sudden and fatal termination. Internally saline laxatives and alkalies to reduce the usual hyperacidity of the urine and increase the quantity are indicated. My patient, Case II., felt that he knew when an attack was coming on by the increased hyperacidity of his urine, and at once began to take alkalithia, which he thought lessened the frequency and mitigated the severity of his attacks, though it did not prevent them.

It would seem to be a sensible thing to treat and remove, if possible, between attacks any local disease that may exist in the throat or upper air passages, with a view to removing the localization of the acute circumscribed œdemas in these areas. It is doubtful if this would accomplish such a highly desirable result, but it certainly should be attempted.

REFERENCES.

1. Collins. Reference Handbook of Medical Sciences, second edition.
2. Strübing. Moritz Schmidt. Die Frankheiten der oberen Lüftwege.
3. Osler. The American Journal of the Medical Sciences, April, 1888.
4. Osler. Ibid., December, 1895.
   Osler. Jacobi Jubilee volume.
5. Osler. The American Journal of the Medical Sciences, January, 1904.
6. Goodale. Posey and Wright, Diseases of the Eye, Ear, Nose, and Throat, p. 690.
7. Bloodgood. Johns Hopkins Hospital Bulletin, May, 1903.
8. Packard. Archives of Podiatrics, October, 1899.
9. Woodbury. Journal of Laryngology, October, 1898.
10. Hallock. Annals of Laryngology, Rhinology, and Otology, November, 1898.
11. Ledderman. The Laryngoscope, September, 1898.
12. Taylor. Philadelphia Medical Journal, April 2, 1898.
13. Chittenden. The American Journal of the Medical Sciences, October, 1898.
14. Ballenger. Journal of Laryngology, Rhinology, and Otology, May, 1896.
15. Griffith. British Medical Journal, June 14, 1902.
16. Morris. The American Journal of the Medical Sciences, November, 1904.
17. Gruss. Crocker, Diseases of the Skin, 1905, p. 156.
18. Morse. Boston Medical and Surgical Journal, February 17, 1898.
19. Halderman. Journal of the American Medical Association.
20. Ninfong. Annals of Otology, Rhinology, and Laryngology, August, 1898.
21. Bishop. Diseases of Nose, Throat, and Ear.
22. Kortright. Brooklyn Medical Journal.

MILK AND SCARLATINA.

By Alice Hamilton, M.D.,
of Chicago.

Milk-borne epidemics of scarlet fever have been reported with more or less frequency ever since the English, during the latter half of the last century, called the attention of the medical profession to this method of spreading the scarlet-fever contagion. Such epidemics have been traced in some instances to the exposure of milk to infection from scarlet-fever patients, in others to milk from cows suffering from a disease supposedly analogous to scarlet fever in human beings. From the first the English have been the ones to lay the greatest stress on the agency of milk in carrying infection, as can be seen from the fact that of 330 epidemics of infectious disease, traced to contaminated milk, no less than 243 have been recorded by English authors (Kober).[1] The usual reason given for this preponderance of milk-borne epidemics in England is that Anglo-Saxons are the only people who drink raw milk to any extent; other European peoples habitually heat or boil their milk (Freeman,[2] Kober, Hall,[3] Jürgensen[4]). It is true that America has reported only 52 epidemics as against the 243 of England, but this is said to be due to laxness of sanitary supervision of the milk supply in this country, and lack of careful search for causes in the presence of epidemics (Freeman). As further proof of the agency of milk